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Hierarchical study of Guyton Circulatory Model

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Abstract: *This article presents an initial study of the Guyton Circulatory Model using BioRica. This model consists of 18 connected modules, each of which characterise a separate physiological subsystem. We have focused the present analysis in the Renin-Angiotensin-Aldosterone System (RAAS). The use of BioRica allowed us to build an hierarchical model for this system by means of directly mapping modules to BioRica nodes. The results of each node were validated by comparison with published results.*

Keywords: Hierarchical Models, Blood Circulation, Renin-Angiotensin-Aldosterone System.

The Guyton model ([1]) is an extensive mathematical model of human circulatory physiology, that characterises relations between conditions and physiological responses. Initially it defined relations between cardiac output and central venous and right atrial pressure, and was extended over time to include many physiological control processes. The Guyton Circulatory Regulation model consists of 18 connected modules, each of which characterises a physiological subsystem. Circulation Dynamics is the primary module. This model is naturally hierarchical, but historically has been defined using a flat collection of differential equations. We started analyzing the main points of the renal control of the blood pressure, in particular the Renin-angiotensin-aldosterone system (RAAS). The RAAS is crucial for the model ([2], [3]) and therapeutic manipulation of this pathway is very important in treating hypertension and heart failure. In general terms, a sustained fall in blood pressure causes the kidneys to secrete renin. This hormone stimulates the production of angiotensin in the circulation, which causes blood vessels to constrict, and stimulates the adrenal gland to produce aldosterone. This causes the tubules of the kidneys to retain sodium and water resulting in increased blood pressure. The mechanism of autonomic nervous controls of salt and water balance by the ADH (antidiuretic hormone) is also included. In this study we obtain, implement and test a true hierarchical model of the RAAS using BioRica. Our final goal is to build a more extensive model.

BioRica ([4]) is a high-level modeling framework developed by the MAGNOME team of INRIA that extends AltaRica ([5]) for biological applications, integrating discrete, continuous, stochastic, non deterministic and timed behaviors in a non-ambiguous way. The main advantage of using BioRica is that allows the characterisation of hierarchical relations between nodes by means of dataflow links, leading to more expressive designs that can be more easily understood. Each module of the Guyton model that is associated to the RAAS was mapped into a BioRica node. We obtained the BioRica RAAS model, the hierarchical set of nodes and input-output relations between them. The nodes that were coded are: Angiotensin control, Aldosterone control, Antidiuretic hormone control (ADH mechanism), Electrolytes and cell water, Thirst and drinking and Kidney.

Each one of these nodes was either directly implemented in BioRica, or by encapsulating Matlab scripts that are used like SBML simulators. The implementations of each node were validated

by comparing its simulations results with results from the Physiome Project (see [6]), which were obtained using JSim (<http://www.physiome.org/jsim/models/cellml/>). Statistical analyses, Student's *t*-test (a parametric hypothesis test) and Kolmogorov-Smirnov for comparing two distributions (a nonparametric hypothesis test) were used to demonstrate that the values in simulation results are not significantly different. The parameters that are external to the *RAAS* were fixed according to the default values of the Physiome Project.

The challenge is how to test the integration of the nodes into the hierarchical model. The first step was analyzing the physiological interpretation of the nodes of the BioRica *RAAS* model. According to biological knowledge the system is activated when there is a loss of blood volume. Specialized cells (macula densa) of distal tubules sense the amount of sodium and chloride ions in the tubular fluid, and if it is low then renin is secreted, stimulating the production of Angiotensin. This process is represented in *Angiotensin node*. Angiotensin causes the secretion of Aldosterone, its production and functions is represented in *Aldosterone node*. Angiotensin also produces the blood vessels constrict, resulting in increased blood pressure, control that is represented by the relation *ANM* (multiplier effect of angiotensin), *MDFLW* (rate of flow of fluid in the renal tubules at the macula densa) between *Angiotensin* and *Kidney node*. Aldosterone causes the tubules of the kidneys to retain sodium and water controlling the blood pressure. The *Kidney* inputs *AMK* (multiplier effect for control of potassium transport through cell membranes) and *AMNA* (multiplier effect for control of sodium) generated by *Aldosterone node* are used to compute the control of *Na* concentration, excretion of potassium and urine production by means of the outputs *NOD* (Na reabsorption), *KOD* (*K* secretion) and *VUD* (volume of urine). Another control process corresponds to the secretion of vasopressin, antidiuretic hormone (*ADH*) that promotes the reabsorption of fluid in the kidneys. The secretion of Antidiuretic hormone is represented by *Antidiuretic node*, linked with *Kidney node*. The production of vasopressin induces the reabsorption of water in the kidneys (*Thirst node*). In *Electrolytes node* is computed the concentration of *K* and *Na* by means of volume of fluid (*TVD* and *VUD* coefficients), rate of reabsorption of sodium *NOD* and rate of secretion of potassium *KOD*.

The second step was studying simulations. The direct effects of Angiotensin and the functions of Aldosterone and Antidiuretic hormone were reviewed by means of the inspection of the equations, relations and simulations. To test the results of the model we checked the control of the rate of flow of fluid in the renal tubules sensed by the macula densa, as one hoped it is taken to its normal level when initial level is low or high.

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